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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,026	07/30/2001	Rosanne M. Crooke	ISPH-0588	1035

36441 7590 09/09/2003

MARY E. BAK
HOWSON AND HOWSON, SPRING HOUSE CORPORATE CENTER
BOX 457
SPRING HOUSE, PA 19477

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/918,026	CROOKE ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the corresp ndence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10 and 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 3, 2003 has been entered.

Claims 1, 2, 4-10 and 12-14 are pending in the instant application.

Claim 1 has been amended.

Claims 1, 2, 4-10 and 12-14 have been examined on the merits.

Information Disclosure Statement

The Information Disclosure Statement, filed March 31, 2003 in Paper No. 13 is acknowledged. However, the Japanese Abstract listed as reference AD and BQ on PTO form 1449 has not been considered because it is in a foreign language and no translation was provided.

Response to Arguments

Applicants Amendment and Response filed July 31, 2003 in Paper No. 15 is acknowledged. Applicants Revocation of Power/Attorney, filed May 13, 2003 in Paper No. 14 is acknowledged.

Rejections and/or objections not reiterated from the previous office action mailed May 1, 2003 in Paper No. 12 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cases et al. [WO 99/67368] in view of Bennett et al. [U.S. Patent No. 6613567] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule targeted to human acyl CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3), wherein said compound hybridizes with and inhibits the expression of human acyl CoA

cholesterol acetyltransferase-2 by at least 40%. Claims 2, 4-10 and 12-14 depend from claim 1 and include all the limitations of claim 1, wherein the compound is an antisense oligonucleotide, and wherein the antisense oligonucleotide comprises modified bases.

Cases et al. teach a method for inhibiting the activity of acyl CoA cholesterol acyltransferase-2 (ACAT-2) via an agent that inhibits the activity of ACAT-2 (see Claim 9 and SEQ ID NOs. 2 and 4), for example. It is noted that the ACAT-2 disclosure of Cases et al. is 100% identical to SEQ ID NO: 3 of the instant invention (see Cases et al. SEQ ID NO: 2). Cases et al. further teach the agent may be an antisense compound which down-regulates the expression of ACAT-2 in cells, for example (see page 24, last paragraph and page 28, lines 15-27). Cases et al. finally teach the antisense compound will be generally about 20 nucleotides in length (see page 28, last paragraph) and may have chemical modifications, including a phosphorothioate linkage or 2'-O-methyl sugars (see page 29, last two paragraphs).

Cases et al. does not teach a compound targeted to a coding region of a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 (SEQ ID NO. 3), wherein said compound hybridizes with and inhibits the expression of human acyl CoA cholesterol acetyltransferase-2 by at least 40%, or antisense oligonucleotide comprising at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound 8 to 80 nucleobases in length targeted to a nucleic acid molecule encoding acyl CoA cholesterol acyltransferase-2 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Bennett et al. teach antisense oligonucleotides that can specifically hybridize with different regions in a target gene, including a 5'-untranslated region, a stop codon region, a coding region, or a 3'-untranslated sequence (see column 3, lines 57-67 and column 4, lines 1-62 and Tables 1 and 2). Bennett et al. further teach a wide range of antisense oligonucleotides that inhibit gene expression at various inhibition capacities (see Tables 1 and 2). Bennett et al. further teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, lines 38-67 and column 7, lines 1-14)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see column 8, lines 13-44)... with modified nucleobases, such as 5-methylcytosine (see column 8, lines 62-67 and column 9, lines 1-14). Bennett et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 10, lines 25-54). Bennett et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have made and used antisense oligonucleotides 8 to 50 nucleobases in length targeted to a coding region of a nucleic acid molecule targeted to human acyl CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3), wherein said compound hybridizes with and

inhibits the expression of human acyl CoA cholesterol acetyltransferase-2 by at least 40%; wherein said compound is an antisense oligonucleotide; wherein said antisense compound comprise a modified internucleoside linkage that is a phosphorothioate linkage, a modified 2'-O-methoxyethyl sugar moiety, a modified nucleobase that is 5-methylcytosine and wherein the oligonucleotide is a chimeric oligonucleotide. One of ordinary skill in the art would have been motivated to make antisense oligonucleotides targeted to a coding region of a nucleic acid molecule targeted to human acyl CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3) using the sequence taught by Cases et al. and the method taught by Bennett et al. One of ordinary skill in the art would have expected success in making antisense oligonucleotides that inhibit acyl CoA cholesterol acyltransferase-2 by at least 40% since Bennett et al. demonstrate that following generic teachings of making antisense oligonucleotides to a target, it would be expected that oligonucleotides will inhibit by at least 40% since a wide range of oligonucleotides of various capacities are created (see Bennett et al. Tables 1 and 2). One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides because Bennett et al. and Fritz et al. taught antisense oligonucleotides with modified bases confer increased nuclease resistance, increased uptake in cells and increased binding affinity for an mRNA target.

It is noted that there is no evidence of record to show any such differences between the acyl CoA cholesterol acyltransferase-2 sequence of Cases et al. (see Cases et al. SEQ ID NO: 2) and SEQ ID NO:3 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to a coding region of acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3) of the instant invention, since designing antisense oligonucleotides was well known in the art at the time of filing.

Applicant's arguments, filed July 31, 2003 have been carefully considered. Applicants argue that claim 1 is now amended to recite antisense oligonucleotides that inhibit acyl CoA cholesterol acyltransferase-2 by at least 40%. Applicants argue that neither Cases et al. Baracchini et al. or Fritz et al. teach or suggest inhibiting acyl CoA cholesterol acyltransferase-2 by at least 40%. Applicants point out that Table I lists antisense sequences that may hybridize to the acyl CoA cholesterol acyltransferase-2 coding region, but some antisense sequences provide no inhibition or low levels of inhibition. Applicants contend that this information supports the fact that generic teachings directed to antisense oligonucleotides targeted to acyl CoA cholesterol acyltransferase-2 do not provide sufficient teachings to suggest the present invention. Applicants also argue that the combined references suggest that antisense oligonucleotides targeted to acyl CoA cholesterol acyltransferase-2 are obvious to make, but obvious is not a standard for patentability. Applicants further argue that the suggestion in the prior art to modify antisense oligonucleotides does not suggest the claimed invention. Applicants argue that the combination of the references do not provide any expectation of success of making antisense oligonucleotides that inhibit acyl CoA cholesterol acyltransferase-2 by at least 40%.

Applicant's arugments have been considered, but are not considered persuasive because the criteria for a 103 rejection is based on three factors: (1) obviousness (2) motivation and (3) expectation of success. In totality, the references render the instant application obvious and demonstrate that one of ordinary skill in the art would have been motivated and expected success in making and using the current invention at the time of filing. As argued above, it would have been *obvious* at the time the invention was made for one of ordinary skill in the art to have made and used antisense oligonucleotides 8 to 50 nucleobases in length targeted to a coding region of a

nucleic acid molecule targeted to human acyl CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3), wherein said compound hybridizes with and inhibits the expression of human acyl CoA cholesterol acetyltransferase-2 by at least 40%; wherein said compound is an antisense oligonucleotide; wherein said antisense compound comprise a modified internucleoside linkage that is a phosphorothioate linkage, a modified 2'-O-methoxyethyl sugar moiety, a modified nucleobase that is 5-methylcytosine and wherein the oligonucleotide is a chimeric oligonucleotide. One of ordinary skill in the art would have been *motivated* to make antisense oligonucleotides targeted to a coding region of a nucleic acid molecule targeted to human acyl CoA cholesterol acetyltransferase-2 (SEQ ID NO: 3) using the sequence taught by Cases et al. and the method taught by Bennett et al. One of ordinary skill in the art would have *expected success* in making antisense oligonucleotides that inhibit acyl CoA cholesterol acyltransferase-2 by at least 40% since Bennett et al. demonstrate that following generic teachings of making antisense oligonucleotides to a target, it would be expected that oligonucleotides will inhibit by at least 40% since a wide range of oligonucleotides are created with various inhibition capacities, including, for example, 0%, 14%, 36%, 49%, 68%, and 84% (see Tables 1 and 2). One of ordinary skill in the art would have been *motivated* to modify the antisense oligonucleotides because Bennett et al. and Fritz et al. taught antisense oligonucleotides with modified bases confer increased nuclease resistance, increased uptake in cells and increased binding affinity for an mRNA target. As further noted above, there is no evidence of record to show any such differences between the acyl CoA cholesterol acyltransferase-2 sequence of Cases et al. (see Cases et al. SEQ ID NO: 2) and SEQ ID NO:3 of the instant invention that would have resulted in an artisan not being able to successfully design and use antisense oligonucleotides targeted to

a coding region of acyl CoA cholesterol acyltransferase-2 (SEQ ID NO:3) of the instant invention, since designing antisense oligonucleotides was well known in the art at the time of filing. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time of filing.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
September 4, 2003

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER